COX-2 selective NSAIDs

Key messages

- COX-2 selective NSAIDs are not more effective than conventional NSAIDs
- COX-2 selective NSAIDs have the same range of adverse effects as other NSAIDs
- COX-2 selective NSAIDs have a lower relative risk of serious gastrointestinal complications but the absolute benefits are small
- As with all NSAIDs, start at the lowest dose and modify the dose according to the individual’s response
- COX-2 selective NSAIDs are approved for osteoarthritis and rheumatoid arthritis only
- Paracetamol is first-line drug therapy for most patients with osteoarthritis

Are you prescribing COX-2 selective NSAIDs as first-line therapy?

Choosing the most appropriate medicine should take into account:
- the clinical condition being treated
- the potential risks and benefits of treatment
- drug dosage
- the length of treatment
- cost.

The rapid uptake in prescribing of the new COX-2 selective NSAIDs—celecoxib (Celebrex®) and rofecoxib (Vioxx®)—has been unprecedented. Data from a sample of GPs in the General Practice Research Network has revealed that 43% of patients prescribed celecoxib for the first time in the three months following its Pharmaceutical Benefits Scheme (PBS) listing had not received a prescription for any analgesic in the previous 12 months. Six months later, the proportion of patients prescribed celecoxib for the first time who had not received an analgesic prescription in the previous 12 months had increased to 59%.

The original cost projections for celecoxib at the time it was listed on the PBS were in the order of $40 million in the first year. Celecoxib prescriptions processed in its first year on the PBS have actually cost over $170 million. To this figure, a further $18 million for the first six-months’ subsidised prescribing of rofecoxib can be added.
Are you prescribing more COX-2 selective NSAIDs than conventional NSAIDs?

COX-2 selective NSAIDs are not more effective than conventional NSAIDs

Celecoxib and rofecoxib were no more effective than comparator NSAIDs in clinical trials.\(^4\,5\)

There is no advantage in converting a patient at low risk of serious gastrointestinal complications and who is responding to their current NSAID therapy to a COX-2 selective NSAID.

COX-2 selective NSAIDs have a similar profile of adverse effects as other NSAIDs

COX-2 selective NSAIDs should not be thought of as ‘NSAIDs without side-effects’ and ‘safe’ to use in those patients in whom you would not otherwise prescribe an NSAID.

Potential adverse effects, including dyspepsia, abdominal pain, nausea and diarrhoea, occur with similar frequency for both COX-2 selective NSAIDs and conventional NSAIDs. Serious gastrointestinal complications can also occur with celecoxib and rofecoxib\(^7\) although the risk is lower than with traditional NSAIDs.

As with all NSAIDs, caution is advised when considering a COX-2 selective NSAID in patients with renal or cardiac disease. Oedema and hypertension with celecoxib and rofecoxib have been reported. Furthermore, a four-fold increase in the rate of myocardial infarction for rofecoxib compared to naproxen in the VIGOR study\(^5\) raised concerns of a prothrombotic effect with COX-2 enzyme inhibition. Whether or not COX-2 selective NSAIDs are prothrombotic remains to be determined. As a precaution, it is prudent to avoid their use in patients who have a thrombotic tendency.

Additionally, celecoxib (which contains a sulfonamide moiety) is associated with skin reactions including rash and urticaria; these accounted for the highest proportion of suspected adverse reactions notified to the Adverse Drug Reactions Advisory Committee (ADRAC) in the first six months following marketing.\(^6\)

COX-2 selective NSAIDs are approved for osteoarthritis and rheumatoid arthritis only

In Australia, celecoxib is approved for the symptomatic treatment of osteoarthritis and rheumatoid arthritis while rofecoxib is approved for the symptomatic treatment of osteoarthritis only.

Although there is some evidence for their use in dental pain and dysmenorrhoea, neither drug is approved for use in these conditions nor for use in gout or acute musculoskeletal injuries (strains and sprains).

The risk of gastrointestinal complications with occasional NSAID use for acute pain at low or intermediate doses is small.\(^4\) There is no evidence to suggest that celecoxib or rofecoxib are preferable to conventional NSAIDs in these circumstances.
Are you prescribing COX-2 selective NSAIDs in those most likely to benefit?

COX-2 selective NSAIDs have a lower relative risk of serious gastrointestinal complications but the absolute risk of such complications is low such that the benefits over other NSAIDs are small.

The CLASS1 and VIGOR5 studies estimated the annual incidence of serious gastrointestinal complications with NSAID use to be around 1.4% while COX-2 selective NSAIDs reduced the relative risk of such events by about 50%. Using these results, around 130 patients must be treated with a COX-2 selective NSAID for one year to prevent one serious gastrointestinal complication that might have developed with a conventional NSAID.

Patients at high risk have about a 5% chance annually of developing a serious gastrointestinal complication. Therefore, in these patients at higher absolute risk, the potential benefits of COX-2 selective NSAIDs are likely to be greater: around 40 high-risk patients must be treated with a COX-2 selective NSAID for one year to prevent one serious gastrointestinal complication.

In contrast, the incidence of developing a serious gastrointestinal complication in low-risk patients is 0.4%; around 500 low-risk patients must be treated with a COX-2 selective NSAID for one year to prevent one serious gastrointestinal complication. The risk in younger, otherwise healthy individuals would most likely be lower still such that they might benefit little from taking a COX-2 selective NSAID rather than a conventional NSAID.

Low-dose aspirin can cause gastrointestinal haemorrhage and should be considered an additional risk factor. In the CLASS study, those taking low-dose aspirin did not show any reduction in gastrointestinal complications with celecoxib compared to conventional NSAIDs. Therefore, low-dose aspirin may offset any potential gastroprotective benefit of COX-2 selective NSAIDs; using more than one NSAID concurrently increases the risk of gastrointestinal adverse events.
Has the dose of NSAID been titrated to effect?

Always start NSAIDs, including COX-2 selective NSAIDs, at the lowest dose and modify according to response.

The response to NSAIDs varies considerably between individuals. Initiate therapy at the lowest dose, adjusting as needed to the minimum effective dose. Adding an intermittent NSAID to regular paracetamol may produce additive benefit and limit the dose of NSAID required.13

Conventional NSAIDs should not be initiated at or near maximum doses (e.g. diclofenac 150 mg/day) in patients (particularly the elderly) at risk of gastrointestinal complications. Similar precautions should be considered when starting a COX-2 selective NSAID.

For example, symptomatic improvement (relative to placebo) was seen in patients with osteoarthritis taking celecoxib 100 mg daily.14 As almost 30% of the study population was older than 70 years of age, this reinforces the notion that reduced doses of NSAIDs can be effective in the elderly.

The figure (right) depicts the volume of prescribing for the different dosage forms of celecoxib and rofecoxib.

Given the above observations, it is interesting to note the consistently low volume of celecoxib 100 mg prescribed.

The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the individual clinical circumstances of each patient.

References:

2. Proof Committee Hansard. Hearings before the Senate Community Affairs Legislation Committee on Consideration of Budget Estimates. (Canberra: May 29, 2001)

Correlation

Tibolone (Livial®) is a steroid with combined oestrogenic, progestogenetic and androgenic properties used for hormone replacement therapy. It is not a selective oestrogen receptor modulator (SERM) as labelled in Prescribing Practice Review 14, Hormone Replacement Therapy. For further information on tibolone see our website under Hormone Replacement Therapy (http://www.nps.org.au).

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